REMARKS

Applicant respectfully requests reconsideration. By this amendment, claims 1, 4-7, 39, 43, 45, 48-51, 71-79, 82-85, 89-102, 104, 108 and 110 have been amended. Claims 3, 41, 42, 44, 46, 47, 80, 81, 86 and 87 have been canceled. Claims 115-121 have been added. Claims 1, 11, 14-32, 38-39, 43, 45, 51-70, 76-77, 82-85, 88, 93, 95-96, 103-104, 107-121 are now pending.

Amended claims 1, 43, 45, 48-51, 82-85, and 108 now specify that the opioid antagonist and/or quaternary derivative of noroxymorphone is methylnaltrexone. Support for this amendment can be found throughout the application as originally filed, for example on page 1, line 8 and in original claims 44, 46, 80, 81 and 86. Consequently, claims 1, 43, 45, 48, 49, 50, 51, 82-85, and 108 have been amended and claims 44, 46, 80, 81 and 86 have been canceled.

Amended claims 1, 51, and 108 no longer recite "free of bioavailable calcium or salts thereof". Support for these amendments may be found on page 1 lines 6 to 8 and page 6 lines 25 to 29. Further support for these amendments can be found on page 13 lines 17 to 19 and page 14 lines 7 to 9.

New dependent claims 116 to 121, introduce the limitation that the pharmaceutical preparation is free of calcium or salts thereof. This amendment finds support in the paragraph which begins on page 23 line 13 of the specification as originally filed, and especially on page 23 lines 15 to 18.

Claims 4-7, 39, 71-79, 89-102 and 104, have been amended to change their dependency and minor typographical errors. Claim 115 has been added, and it repeats features of claims 32 and 88. Support for claim 115 can be found on page 14 line 7 to page 19 line 14 in the original specification as filed.

Claim 110 has been amended to correct a typographical error; a missing period has been added.

Claims 1, 11, 14-32, 38-39, 43, 45, 51-70, 76-77, 82-85, 88, 93, 95-96, 103-104, 107-121 are now pending for examination with claims 1, 51, 85, and 108 being independent claims. No new matter has been added.

Elections/Restrictions

The Examiner has acknowledged the Applicant's election of methylnaltrexone and tegaserod maleate for oral administration in the reply filed on July 31, 2006.

Applicant acknowledges that claims 2-10, 12-13, 33-37, 40, 47-50, 71-75, 78-79, 89-92, 94, 97-102 are now withdrawn. Withdrawn claims 3 and 47 are hereby cancelled. Withdrawn claims 4-7, 48-50, 71-75, 78-79, 89-92, 94, 97-102 are currently amended.

Claim Objections

The Examiner has objected to claims 39, 77 and 96 because of an apparent misspelling. Applicant has amended the claims to correct the misspelling.

Claims Rejection – 35 U.S.C. §102

The Examiner has rejected claims 1, 11, 14, 21, 41-42, 45-46, 51-52, 60 and 80-84 under 35 U.S.C. §102(b) as being anticipated by US Pat. No. 4,176,186 to Goldberg et al. (Goldberg). Applicant respectfully traverses.

Goldberg teaches a method of preventing or relieving the intestinal mobility inhibiting side effects of narcotic analgesics such as methadone by the administration of quaternary derivatives of noroxymorphone, including methylnaltrexone. However, there is no mention in Goldberg of treatment of irritable bowel syndrome (IBS).

IBS is described in the present application at pages 1-2. The pathogenesis of IBS is described at page 2, lines 11-13. IBS is not a disorder resulting from use of narcotic analgesics. Goldberg teaches only treatment of side effects that result from use of narcotic analgesics. Therefore, Goldberg does not teach the use of peripheral opioid antagonists for the treatment of IBS.

When a reference lacks an explicit teaching of a recited claim element, it can nonetheless anticipate the claim if it *inherently* teaches all claim elements. Inherent anticipation requires that the missing element is *necessarily* present in the reference. [IN RE ROBERTSON, 169 F.3D 743, 745 (FED. CIR. 1999), DAYCO PRODS., INC. V. TOTAL CONTAINMENT, INC., 329 F.3D 1358, 1369 (FED. CIR. 2003)] Thus, for the present claims to be inherent in the teachings of Goldberg, it must be the case that the practice of the Goldberg invention necessarily and inevitably results in the claimed invention. Treating a patient for side-effects caused by narcotics does not necessarily and inevitably result in treating IBS, which is unrelated to narcotic use. Thus, Goldberg cannot inherently anticipate the present claims. Respectfully, Applicant requesst that the Examiner withdraw the rejection under 35 U.S.C. §102.

Claims Rejections – 35 U.S.C. §103

The Examiner rejects claims 1, 11, 14-32, 38-39, 41-46, 51-55, 56-70, 76-77, 80-88, 93, 95-96, 103-104 and 107-114 under 35 U.S.C. §103(a) as being unpatentable over US Pat. No. 4,176,186 to Goldberg et al. (Goldberg) in view of US Pat. No. 5,159,081 to Cantrell et al. (Cantrell) and further in view of US Pat. No. 6,986,901 to Meisel et al. (Meisel). Applicant respectfully traverses.

All of the claims pending in the present application have been amended to refer only to a single compound, methylnaltrexone (MNTX). Of the references cited by the Examiner, only Goldberg explicitly mentions MNTX. Goldberg was discussed above. Goldberg does not teach or suggest the use of methylnaltrexone to treat IBS. Goldberg teaches a method of treating the intestinal mobility inhibiting side-effects of narcotic analgesics. Irritable bowel syndrome (IBS) is not a disease or condition caused by narcotic analgesics. Some of the symptoms of IBS might be similar to the side-effects of narcotic analgesics, but others are physiologically opposite. For example, diarrhea can be a symptom of IBS. Therefore, Goldberg teaches a treatment to be used only to counteract a side-effect caused by administration/use of narcotic analgesics.

Cantrell teaches a specific class of compounds, N-substituted piperidine compounds and uses thereof. Even if a person skilled in the art, starting with Cantrell, were to look for further opioid antagonists to test, that person would be inclined to select opioid antagonists similar to piperidines, i.e. those with high infinity for opioid receptors. As evidenced by Brown D.R. in Goldberg, L.I. (1985) *Neuropharmacology* Vol. 24, No. 3, pp. 181-191 (cited in Information Disclosure Statement filed on June 16, 2004; a copy of the reference is enclosed with this response for Examiner's ease of reference), quaternary amine derivatives of opioid antagonists,

for example, methylnaltrexone, generally have greatly diminished affinity for opioid receptors (p. 182, lines 24-41). The compounds taught by Cantrell have "...been found to display excellent activity in an opioid receptor binding assay which measures the affinity of the compounds to bind to mu receptors." (Col 57, lines 27-30). The high affinities for the mu-opioid receptor, ranging in K_i values from 0.26 – 32.40 nM, are shown in Table II (Col 58-59) and they correlate with the capacity of the compounds to displace naloxone from the mu receptor. As discussed in Zimmerman D.M., Gidda J.S., Cantrell B. E. et al. (1994) *J. Med. Chem.* Vol. 37, pp.2262-2265 (cited in an accompanying Information Disclosure Statement; a copy of the reference is enclosed with this response for Examiner's ease of reference), it was appreciated in the art that it would be desirable to develop compounds with high affinity for the mu receptor: "Previous efforts to develop peripherally selective opioid antagonists have primarily focused on quaternization of known opioid antagonists...; however, their *(quaternary opioid antagonists)* usefulness is limited because of low selectivity for peripheral versus central receptors (parent molecule or metabolite) and limited potency (p. 2262, emphasis added)." Indeed, this report reveals that skilled researchers expected quaternary opioid antagonists *not* to have appropriate characteristics. The authors of this report further discuss the N-substituted piperidine compound LY246736:

> "...Compound 3 *(LY246736)* has high affinity for opioid receptors (K_i = 0.77, 40, and 4.4 nM for mu, kappa, and delta receptors, respectively). It is a potent mu receptor antagonist following parenteral and oral administration and distributes selectively (>200-fold selectivity) to peripheral receptors. Thus, 3

(LY246736) has properties suitable for the clinical investigation of mu opioid receptor involvement in GI motility disorders (Abstract, emphasis added)."

Therefore, a person skilled in the art, starting with Cantrell would be inclined to turn to opioid antagonists with high infinity for opioid receptors and would be unlikely to choose methylnaltrexone as a substitute for a piperidine compound.

The Examiner cites Meisel for a teaching of tegaserod for the treatment of IBS and further states that Meisel teach that treatment for gastrointestinal issues includes sedatives, opiates, and antibiotics. The Examiner has also cited Meisel for a disclosure of various oral formulations. Meisel is directed to compositions of amino-ether and/or ester oxides in combination with a gastrointestinal active agent and an anti-inflammatory agent, to prevent or treat diverse gastrointestinal disorders. IBS is listed as one among several disorders (Col 3, lines 1-17). However, Meisel doesn't disclose or suggest a peripheral opioid antagonist in the composition for any purpose. Furthermore, Meisel recommends including an opioid, rather than an opioid antagonist, in IBS therapies.

In summary, Applicant submits that the pending claims directed to the use of methylnaltrexone for treating IBS, as well as the pending claims directed to pharmaceutical preparations and uses of methylnaltrexone in combination with at least one IBS therapeutic are nonobvious in view of the combined teachings of Goldberg, Cantrell, and Meisel.

Respectfully, Applicant requests the present rejection be withdrawn.

CONCLUSION

Claims 1, 11, 14-32, 38-39, 43, 45, 51-70, 76-77, 82-85, 88, 93, 95-96, 103-104, 107-121 are now pending. In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: June 27, 2007
x06/27/2007x

Respectfully submitted,

By _____
Roque El-Hayek, Registration No.: 55,151
Edward R.Gates, Registration No.: 31,616
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000